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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,993	01/12/2001	Richard B. Greenwald	213.1079-CIP3	9994

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/10/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/758,993	Applicant(s) GREENWALD ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,30 and 32-34* is/are rejected.

7)☒ Claim(s) *28,29 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The preliminary amendment filed July 8, 2002 was not entered because it was not accompanied by a marked-up version of the replacement paragraphs showing all the changes relative to the previous version of the paragraphs. See 37 CFR 1.121(b)(1)(iii).

The Sequence Listing filed September 6, 2002 has been approved.

2. The disclosure is objected to because of the following informalities: SEQ ID NOS need to be inserted after the Gly-Phe-Leu-Gly amino acid sequence at page 5, line 7, and page 20, line 13. See 37 CFR 1.821(d). The status of the U.S. patent applications recited at page 2, lines 21-22, and page 14, line 25, needs to be updated. Appropriate correction is required.

3. Claims 1-27, 30, and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At claim 1, line 14, "and" should be inserted before the last occurrence of "substituted" so that standard Markush terminology is used. At claim 6, line 1, the word "about" should be deleted, because use of the word implies that fewer than 2 amino acid residues can be present in the peptide, whereas by definition a peptide requires at least 2 amino acid residues. At claim 9, line 2, "and" should be changed to "or" so that standard Markush terminology is used. At claim 13, line 8, the last two aromatic groups in the line are monovalent, and thus do not appear to be permitted by Formula I as defined in independent claim 1. If these aromatic groups are re-written a divalent groups, Applicants should ensure that they do not duplicate any other aromatic groups recited in the claim. At claim 17, line 4, the word "and" should be inserted after the last comma in the line so that standard Markush terminology is used. The definition of Z in claim 32 is unclear because Z is not always covalently linked to at least one biologically active material. Rather, before the reacting step, Z is linked to the leaving group

La. Also, claim 32 would be clarified if it were amended to recite that after the reaction, Z is covalently linked to "the" at least one biologically active material. To the extent that claim 33 explicitly recites that D can be a leaving group, the claim is indefinite because a leaving group is not the type of substituent which would have been expected to be useful in the treatment of a disease or disorder in an animal. It is not clear that Applicants intended to claim the administration of compounds comprising leaving groups.

4. Claims 1-27 and 30-34 are objected to because of the following informalities: At claim 1, line 19; claim 31, page 55, line 15; and claim 32, page 56, line 14; the word "and" after "nitro-" should be deleted and replaced with a comma. At claim 2, line 11, a comma should be inserted after "R_{14}". A SEQ ID NO needs to be inserted after the Gly-Phe-Leu-Gly amino acid sequence in claim 7. See 37 CFR 1.821(d). At claim 12, line 2, "as" should be deleted. In claim 13, the aromatic groups at line 6, third group, and line 8, third group, are duplicates. At claim 31, line 6, a semicolon should be inserted at the end of the line. At claim 31, page 55, line 21, the word "and" should be deleted. Appropriate correction is required.

5. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Dependent claim 8 indicates that D can be H; however, independent claim 1 requires D to be a leaving group or a residue of a compound to be delivered into a cell. H is not a member of either of these two groups.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claim 8 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-56 of U.S. Patent No. 6,180,095. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '095 patent where B is a protein, polypeptide, peptide, or enzyme (see claims 43-47) anticipate instant claim 8 where Z is a moiety that is actively transported into a target cell, which includes amino acids, and D is H.

8. The effective filing date of instant claims 1-34 is deemed to be January 12, 2001, the filing date of the instant application. Instant claims 1-34 are not deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of parent application 09/183,557 because the parent application, under the test of 35 U.S.C. 112, first paragraph, does not disclose the full scope of Z-$[D]_y$ substituents recited in the instant claims. Accordingly, U.S. Patent No. 6,180,095, which has a different inventorship than the instant application, is available as prior art against the instant claims.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

10. Claim 8 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,180,095. See the above obviousness-type double patenting rejection.

11. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by the Greenwald et al article (J. Med. Chem. Vol. 42, pages 3657-3667). The Greenwald et al article teaches compounds 42 and 43 (see page 3664), which anticipate Applicants' compounds of claim 8 in which Z is a hydrophobic moiety and D is H. The $NHCH(CH_3)_2$ group in the Greenwald et al article's compounds, less one of the hydrogen atoms, corresponds to Applicants' Z group.

12. Claims 1, 2, 4-6, 8, 13, 16-18, 20, 21, 23, 24, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by the Zier et al article. The Zier et al article teaches an octapeptide in which the sidechain of a Glu residue is modified with HO-Bzl-P in order to maintain the solubility of the octapeptide during synthesis. See, e.g., page 1039, first full paragraph and formula (I), and page 1040, Scheme 1, compounds 3 and 4. Note that there is an obvious error in compound 3, in that the reaction of the carboxylic group in compound 1 with the amino group of compound will result in a condensation reaction and not a rearrangement of the carbonyl and amino groups. Accordingly, the modified peptide of the Zier et al article corresponds to Applicants' compound in which Applicants' R_{11} is PEG and is capped with a methyl group, Applicants' m=0, Applicants' M is O, Applicants' n=1, Applicants' R_7 and R_8 are H, Applicants' Y_3 is O, Applicants' p=1, Applicants' Y_2 is NH, Applicants' R_2, R_3, R_5, and R_6 are H, Applicants' r, s, t, and u are 1, Applicants' R_1 and R_4 are H, Applicants' Y_1 is O, Applicants' Y_4 is O, Applicants' y is 1, and Applicants' Z is CH_2 (a hydrophobic group), CH_2-CH_2 (a hydrophobic group), or the glutamic acid residue (an amino acid residue), and Applicants' D corresponds to the remainder of the octapeptide.

13. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being obvious over the Zier et al article. Application of the Zier et al article is the same as in the above rejection of claims 1, 2, 4,

5, 6, 8, 13, 16-18, 20, 21, 23, 24, and 27. The Zier et al article teaches a PEG molecular weight of 550, and does not teach a PEG molecular weight within the ranges recited in instant claims 25 and 26. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal PEG sizes for the modified peptides of the Zier et al article because degree of polymerization is an art-recognized result-effective variable which is routinely determined and optimized in the polymer arts, and because one of ordinary skill in the art would recognize that by increasing the molecular weight the PEG, the solubility of the modified peptide would be increased, a result desired by the Zier et al article.

14. Claims 28 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 31 would be allowable if rewritten or amended to overcome the claim objection set forth in this Office action. Claim 32 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and the claim objections set forth in this Office action. Claims 3, 7, 9-12, 14, 15, 19, 22, 30, 33, and 34 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

With respect to instant claims 3, 7, 9-12, 14, 15, 19, 22, 28, and 29, the prior art of record does not teach or suggest compounds having the structures recited in these claims. With respect to instant claim 30, the Zier et al article does not teach its PEG-modified peptide in combination with a carrier acceptable for in vivo administration to an animal. Because the Zier et al article does not teach or suggest a pharmaceutical or diagnostic use for its peptide, there is no

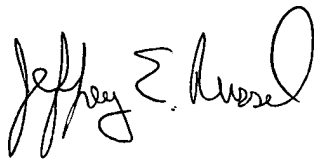
motivation to combine the PEG-modified peptide of the Zier et al article with such a carrier. With respect to instant claims 31 and 32, in view of the synthesis method taught by the Zier et al article (see page 1040, Scheme 1) in which a glutamic acid sidechain is modified with HO-Bzl-P, there is no motivation to use a starting compound having Applicants' Formula III or V, in which case an intact glutamic acid residue would not exist until completion of the reacting step. With respect to instant claims 33 and 34, the Zier et al article does not teach the in vivo administration to an animal of its PEG-modified peptide, and because the Zier et al article does not teach or suggest a pharmaceutical or diagnostic use for its peptide, there is no motivation to administer the PEG-modified peptide of the Zier et al article to an animal.

The Greenwald et al article (J. Med. Chem. Vol. 42, pages 3657-3667) has been carefully considered with respect to its disclosure of compound 41 (see page 3664, Table 3); however, the -O^{t}Bu group does not constitute a leaving group as commonly defined in the art, and accordingly the compound does not anticipate or suggest the instant claimed invention.

Bosslet et al (U.S. Patent No. 5,877,158) is cited as art of interest, but is not deemed to teach or suggest the instant claimed invention. In particular, the compounds of Formula III at columns 3-4 are noted; however, these compounds do not comprise a group corresponding to Applicants' Z group because the aminohexopyranosyl group forms part of Bosslet et al's drug, doxorubicin, and cannot fairly be described as forming a group separate from the drug.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

December 9, 2002